529 Rec'd PCT/PTO 11 JUL 2000

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	ATTORNEY'S DOCKET NUMBER 1029/00205
	U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 09/600073

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR99/00040	12 January 1999	12 January 1998

TITLE OF INVENTION
METHOD FOR EXPLORING AND DISPLAYING TISSUE OF HUMAN OR ANIMAL ORIGIN FROM A HIGH-FREQUENCY ULTRASOUND PROBE

APPLICANT(S) FOR DO/EO/US
SAIED, Amena, BERGER, Geneviève, LAUGIER, Pascal, PUECH, Michel

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. § 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3).

9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. ☒ A translation of the Annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☒ A substitute specification.

15. ☐ A change of power of attorney and/or address letter

16. ☒ Other items or information:

Copy of the PCT Request; International Search Report with English translation; International Preliminary Examination Report

532 Rec'd PCT/PTO

U.S. APPLICATION NO (If known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/600073	PCT/FR99/00040	1029/00205

☒ The following fees are submitted:

	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO.....**$840.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) **$670.00**		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2))....**$760.00**		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....**$970.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....**$96.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$840.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$130.00**	

Claims	Number Filed	Number Extra	Rate		
Total Claims	10 - 20 =	0	X **$18.00**	**$0.00**	
Independent Claims	1 - 3 =	0	X **$78.00**	**$0.00**	
Multiple dependent claim(s)(if applicable)			+ **$260.00**	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$970.00**	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28)				**$0.00**	
SUBTOTAL =				**$970.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				**$0.00**	
TOTAL NATIONAL FEE =				**$970.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				**$0.00**	
TOTAL FEES ENCLOSED =				**$970.00**	
				Amount to be: refunded	**$**
				charged	**$**

a. ☒ A check in the amount of $970.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. **22-0185** in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Director is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **22-0185**. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b) must be filed and granted to restore the application to pending status

SEND ALL CORRESPONDENCE TO:

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1990 M Street, N.W., Suite 800
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Morris Liss 7/11/00
SIGNATURE

Morris Liss
NAME

24,510
REGISTRATION NUMBER

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	Does not match with the original claims. does match with Sub. Spec.
Amena Saied et al.	:	
Serial No.: To be assigned	:	Art Unit: To be assigned
Filed: Herewith	:	Examiner: To be assigned
For: METHOD FOR EXPLORING AND DISPLAYING TISSUE OF HUMAN OR ANIMAL ORIGIN FROM A HIGH FREQUENCY ULTRASOUND PROBE	:	Atty Docket: 1029/00205

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-captioned national phase application as follows.

IN THE CLAIMS

Kindly amend claims 3, 4, 5, and 6 as follows:

At claim 3, lines 1-2, replace "either of Claims 1 and 2" with --Claim 1--.

At claim 4, lines 1-2, replace "any one of the preceding Claims" with --Claim 1--.

At claim 5, lines 1-2, replace "any one of the preceding Claims" with --Claim 1--.

At claim 6, line 2, replace "any one of the preceding claims" with --Claim 1--.

REMARKS

The claims have been amended to eliminate multiple dependency and to improve their format. None of these amendments is believed to involve any new matter. Accordingly, it is respectfully requested that the foregoing amendments be entered, that the application as so amended receive an examination on the merits, and that the claims as now presented receive an early allowance.

Respectfully submitted,

Morris Liss

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Date: 7/11/00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	
	:	
Amena Saied et al.	:	
	:	
Serial No.: To be assigned	:	Art Unit: To be assigned
	:	
Filed: Herewith	:	Examiner: To be assigned
	:	
For: METHOD FOR EXPLORING AND DISPLAYING TISSUE OF HUMAN OR ANIMAL ORIGIN FROM A HIGH FREQUENCY ULTRASOUND PROBE	:	Atty Docket: 1029/00205

SUBMISSION OF SUBSTITUTE SPECIFICATION

Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants submit herewith a substitute specification for examination in the above-identified national phase application.

Respectfully submitted,

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Date: 7/11/00

Process for the investigation and display of tissues of human or animal origin using a high-frequency ultrasound probe

The present invention relates to a process for the investigation and display, using ultrasound echography techniques, of tissue structures of human or animal origin such as in particular the ocular globes and more particularly of the posterior segment (the vitreous cavity, the posterior wall of the globe lined by the choroid and the retina, the macula), tissue structures of the anterior segment (the cornea, the anterior chamber, the iris and the crystalline lens). The invention also relates to a device and an ultrasound probe which allow this investigation and this display to be achieved in 2D or 3D.

In ultrasound imaging and more particularly in medical echography, the choice of frequency is dictated by the compromise between resolution and penetration depth. Specifically, because of the increase in attenuation of ultrasound waves with frequency, the penetration depth of ultrasound increases with decreasing frequency. However, the image resolution decreases with decreasing frequency.

In addition, a process for the investigation and display of human tissues is known, through document US A 5,178,148, for determining the volume of a tumour or of a gland using signals coming from a probe steered by the process.

Processes are known, in particular through patent FR 2,620,327, for the investigation of ocular structures, by echography, using probes operating at low frequencies of the order of 10 MHz, and focused to a depth roughly equal to the size of an ocular globe (about 23 to 25 mm). These processes mean, on one hand, that images in section of the posterior segment of the

eye can be achieved with spatial resolutions of the order of a millimetre and, on the other hand, that a very rough examination of the entire anterior segment of the eye can be carried out.

The major drawback of low-frequency echography is mainly the low resolution (600 to 700 μm) provided by these low frequencies, which do not allow detailed analysis of the retina and the other layers of the posterior wall of the eye (choroid and sclera) and more particularly in the macular region.

In order to increase both the lateral and axial resolution, investigation and display processes using ultrasound probes at high frequency, of the order of 50 to 100 MHz (cf. US 5,551,432 and C.J. PAVLIN, M.D. SHERAR, F.S. FOSTER: "Subsurface ultrasound microscopic imaging of the intact eye", Ophthalmology 97: 244, 1990), with a short focal length (of about 4 to 8 mm), have enabled the use, with a resolution of 50 μm, of structures of the anterior segment of the eye, to depths of the order of 5 mm, or of structures of the peripheral retina which are very close to the anterior segment.

In conclusion, it is therefore accepted that the use of high frequencies seems to be limited to investigation of the anterior segment and the peripheral retina, whereas investigation of the deep structures (posterior segment) requires the use of much lower frequencies, while only providing very low spatial resolutions, of a few hundred microns.

The present invention aims to alleviate the drawbacks of the known processes of the prior art, by proposing an investigation and display process using a high-frequency ultrasound probe which combines both very high spatial resolution and a field of investigation covering the anterior and posterior segments of the ocular globe.

To this end, the process for the investigation and display of tissues of human or animal origin is characterized in that:

- an ultrasound probe is positioned, said probe being carried by a head steered by means of a three-dimensional positioning system, in particular a system controlled by a computer at right angles to said tissue structure,

- the probe is controlled such that it generates beams of convergent high-frequency ultrasound waves whose nominal frequency is included within the range from 30 to 100 MHz with a broad bandwidth, adapted to the frequencies reflected by the structure investigated, these waves being focused on a given area of tissue structure,

- the tissue structure is scanned by the positioning system steered by the computer, while said computer carries out, in parallel, the acquisition of the signals reflected by the tissue structure,

- various signal processing operations are carried out on the data coming from the scanning, to improve the reproduction of the information and to facilitate the interpretation thereof by the practitioner.

According to another advantageous characteristic of the invention, the probe is excited such that it generates wave beams whose nominal frequency is included within the range from 30 to 100 MHz with a broad bandwidth, adapted to the frequencies reflected by the structure investigated.

According to yet another advantageous characteristic of the invention, the wave beams are focused over a vertical penetration distance of between 20 and 30 mm.

Other characteristics and advantages of the present invention will emerge from the description given hereinbelow, with reference to the appended drawings which illustrate an entirely non-limiting embodiment of the invention. In the figures:

- Figure 1 is a synoptic view of a device enabling the process forming the subject of the invention to be implemented;

- Figure 2 is a view illustrating a use of the process forming the subject of the invention for the investigation of the posterior segment of an ocular globe;

- Figure 3 is a view illustrating a use of the process forming the subject of the invention for the investigation of the anterior segment of an ocular globe;

- Figures 4a and 4b illustrate, on one hand, a front view of one embodiment of the ultrasound probe

consisting of an annular array whose focus point can be modified electronically and, on the other hand, a side view of this same probe into which a phase difference has been introduced at transmission or at reception between the various rings making up the array;

- Figure 5 is a view illustrating a use of the process forming the subject of the invention for the investigation of the anterior segment of an ocular globe, using a dynamic focusing probe;

- Figure 6 is a view illustrating a use of the process forming the subject of the invention for the investigation of the posterior segment of an ocular globe, using a dynamic focusing probe;

- Figure 7 shows a comparison between a macular section of a human globe *in vitro*, obtained by macroscopic histological imaging (right side) and an image arising from the process forming the subject of the invention (left side) where P represents the retinal folds, R the retina, S the sclera and V the vitreous humour;

- Figure 8 is the image obtained from an anterior segment of a rabbit's eye, by the process forming the subject of the invention, where C represents the cornea, I the iris, S the sclera and Cr the anterior surface of the lens.

According to a preferred embodiment of the process forming the subject of the invention, of which one system enabling its implementation is shown schematically in Figure 1, the process consists in positioning an ultrasound probe 1 mounted within a head articulated in three dimensions X, Y, Z, at least one direction of which can be fixed, this head being steered by a servo-controlled positioning system 2, controlled by a computer 3, in particular in a direction perpendicular to the medium to be investigated.

This ultrasound probe 1 consists mainly of a transducer, in particular one made of PVDF (polyvinylidene difluoride), controlled by a

transmitter receiver 4, in order to generate beams of convergent, broadband, ultrasonic waves, these waves being able to adopt a spherical or linear profile.

Next, Figure 2 shows an investigation of the posterior segment of an ocular globe 5, previously inserted into a coupling medium 6 which does not impair the propagation of the waves, especially in the retina region. A probe 1 positioned on the pars plana 7 is used to avoid absorption of the ultrasound beam by the lens 8 (this lens also marking the boundary between the posterior segment 9 and the anterior segment 10 of an ocular globe 5). This probe 1 transmits beams of ultrasound waves set within a nominal broadband frequency range varying from 30 to 100 MHz, involving wavelengths going from 50 to 15 µm, focused at a focal length of between 20 and 30 mm and preferably 25 mm, corresponding in fact to a focus at an average depth of an ocular globe.

For example, for a probe with a nominal frequency of 50 MHz, lateral and axial resolutions of 220 and 70 µm respectively are obtained at the focal length.

The receiving system will have a bandwidth adapted to the frequencies reflected by the structure, these frequencies being lower than the transmitted frequencies because of the attenuation by the medium which is crossed.

In order to investigate the anterior segment (cf. Figure 3), this same probe 1 is used under the same control conditions as previously, in a position offset on the vertical axis (Z axis) at a distance corresponding in fact to the previous focal length.

According to another embodiment, the focal length, especially on the vertical penetration axis, is not modified by a mechanical servocontrol 2 in the position, but by an electronic or digital device steering the probe and able to modify, by careful command, the focusing area of the probe, in order thus to obtain simultaneously a high resolution image of the anterior segment and of the posterior segment of the eye. This probe, with dynamic focusing carried out by an electronic or digital control process, consists of a multi-element probe, with circular symmetry, made up of several concentric annular transducers evenly spaced over a plane surface or with spherical concavity (refer to Figure 4a). These transducers are independent of each other and are controlled individually in transmission and in reception by pulses which are offset in time (refer to Figure 4b which shows dynamic focusing obtained by introducing a phase difference - time delay - into the transmission between the various rings).

In transmission, the generated wavefront is convergent and its curvature is modified according to the distance between the structure investigated and the probe. The peripheral rings transmit first and the excitation of the central ring is the most retarded. Thus the focal length along the axis of the probe can be varied and is therefore determined by the phase difference or the time delay introduced between the various transducers. The same principle of dynamic focusing is used in reception: the electronic delay is adjusted to the depth of the echoes which arrive at that moment at the probe. In this way the depth of field is increased without in any way degrading the lateral resolution.

A measurement system, of which each of the components (digitizer 11, computer 3, control electronics 2, transmitter/receiver 4, etc.) forming it has a bandwidth compatible with the processing and analysis of the signals originating from the anterior

segment and/or of the signals coming from the posterior segment of the eye, enables processing of the signals backscattered by the structure investigated. Thus, the backscattered ultrasound signal is amplified then digitized using the digitizer 11, at a given sampling frequency (in particular of the order of 400 MHz over 8 bits).

This same computer controls the stepper on DC motors in order to move the probe and scan the ultrasound beams over the sample in a defined step along X and along Y in order to allow another measurement point or in an R,Ω step using a probe support head which allows an arciform scan.

For *in vivo* measurements and investigations, it is necessary, in order to get round the problem of parasitic movements of the eye in its orbit, to process the signal in real time and to have available an extremely fast and accurate probe movement system.

According to another characteristic, the computer is fitted with a module for processing the image and the radiofrequency signal. This module has programmed software which enables the two quantitative approaches, of 2D and/or 3D biometry and of tissue characterization, to be carried out.

The echographic signal can be shown in real time in the form of a A-scan line or in the form of a 2D image of the B-scan type. The B-scan images can display sections in the various planes parallel to the direction of propagation of the ultrasound (cf. Figures 7 and 8). A 2D image of the C-scan type can also be calculated in order to display sections in the plane perpendicular to the direction of propagation of the ultrasound. The C-scan is able to show sections located at different depths of the whole ocular globe.

The calculation and the reconstruction of the 3D image can be carried out using programmed mathematical functions specific to the ultrasound data to be processed.

Thus, provided the propagation speed of the ultrasound in the structures investigated is known, it is possible to determine morphological characteristics of these structures, especially their thickness and/or their volume.

The processing software of the radiofrequency signal enables a frequency analysis of the digitized and recorded backscattered signals to be made in order

to calculate quantitative ultrasound parameters for the purpose of tissue characterization. These parameters are in particular the attenuation coefficient in dB/cm.MHz (decibels/cm.megahertz), the overall attenuation coefficient in dB/cm, the backscatter coefficient in dB/cm.MHz and the overall backscatter coefficient in dB/cm.

These parameters can be estimated locally and their values can be shown in the form of images (parametric images).

It is of course possible to add other algorithms for processing the radiofrequency signal and the image, algorithms which could produce quantitative morphological and/or tissue information capable of characterizing the structures of the eye.

The images obtained by this investigation process, both for an ocular globe and the region of the anterior segment and the posterior segment, have a resolution which is improved by a factor of at least two to three compared with that obtained with conventional echographs and are not limited by the transparency of the media investigated as in particular with conventional optical investigation means (biomicroscopy, angiography) whose quality can be affected by the presence of cataracts and haemorrhages.

By way of example, Figure 7 illustrates the similarities between a histological image and an echographic image of the macula of a human eye (*in vitro*), and Figure 8 illustrates an image of an anterior segment of a rabbit's eye.

The process and the device which enables its implementation, such as those described previously, are not limited to applications in ophthalmology, but they can also find applications in gynaecology and obstetrics, in gastro-enterology and in the field of cardio-vascular examinations and examinations by coelioscopy, or in dermatology and more generally in any medium which reflects a usable signal.

In particular, in the field of dermatology, it is possible, using the investigation and display process forming the subject of the invention, to investigate the various thicknesses of tissue forming the skin. Thus, it is possible for example, by processing the signal, to assess the degree of skin hydration, to evaluate healing of a tissue, to localize and investigate a tumour, and finally, more generally, to to open the way to examining a large number of pathologies currently encountered in dermatology.

The focus point or focusing area of the wave beam will be adjusted within a range going from a few tenths of a millimetre to several millimetres and the waveband used will be between 30 and 100 MHz.

It is of course understood that the present invention is not limited to the embodiments described and shown hereinbefore, but that it encompasses all the variants thereof.

CLAIMS

1. Process for the investigation and display of tissues of human or animal origin, in which:

- an ultrasound probe (1) is positioned, said probe being carried by a head steered by means of a three-dimensional positioning system (2), in particular controlled by a computer (3) at right angles to the said tissue structures,

- the probe is controlled such that it generates ultrasound wave beams,

- the tissue structures are scanned by the said positioning system, which carries out a parallel acquisition of the signals reflected by the tissue structures, and

- the signals from the data derived from scanning are processed, this process being characterised in that the ultrasound waves generated are convergent, high frequency waves whose nominal frequency is included within the range from 30 to 100 MHz with a large pass band, adapted to the frequencies reflected by the investigated structures, these waves being focused on a given zone of the tissue structures over a vertical penetration distance of between 20 and 30 mm.

2. Process according to Claim 1, characterised in that it is applicable to the investigation of a posterior segment of an ocular globe.

3. - Process according to either of Claims 1 and 2, characterised in that it is applicable to the investigation of an anterior segment of an ocular globe.

4. - Process according to any one of the preceding Claims, characterised in that it is applicable to the investigation of a human ocular globe.

5. - Process according to any one of the preceding Claims, characterised in that it is applicable in gynaecology and obstetrics, in gastro-enterology and in the field of cardio-vascular examinations and

examinations by coelioscopy, or in dermatology and more generally in any medium which reflects a usable signal.

6. System for the implementation of the process according to any one of the preceding claims, comprising an ultrasound probe (1) mounted within a head articulated in three dimensions, controlled by a computer (3), in a direction in particular perpendicular to the medium to be investigated, characterised in that the probe (1) consists of a transducer, controlled by a transmitter/receiver (4), in order on one hand to generate and to focus the convergent, broad band, ultrasonic wave beams, using an electronic or digital focusing device over a vertical distance of between 20 and 30 mm, in the direction of the tissue structures to be scanned and investigated, by means of a coupling medium (6), and on the other hand to collect the signals reflected by the said structures for the purposes of processing in particular by the computer (3) with a view to subsequent interpretation.

7. System according to Claim 6, characterised in that the focal distance of the ultrasound probe (1) is modified by an electronic or digital device in order to adjust the focus point of the said probe.

8. System according to Claim 6, characterised in that the focal distance of the ultrasound probe (1) is modified mechanically by the servo-controlled positioning system (2).

9. System according to Claim 6, characterised in that the computer (3) steers the motors step by step in order to ensure the movement of the probe (1) and the scanning of the ultrasound beams over the tissue structures by a step (R, õ), using a probe support head which allows an arciform scan.

10. System according to Claim 6, characterised in that the computer (3) steers the motors step by step in order to ensure the movement of the probe (1) and the scanning of the ultrasound beams over the tissue

structures by a step (X,Y,Z), using a probe support head which allows a cartesian scan.

Process for the investigation and display of tissues of human or animal origin using a high-frequency ultrasound probe

The present invention relates to a process for the investigation and display, using ultrasound echography techniques, of tissue structures of human or animal origin such as in particular the ocular globes and more particularly of the posterior segment (the vitreous cavity, the posterior wall of the globe lined by the choroid and the retina, the macula), tissue structures of the anterior segment (the cornea, the anterior chamber, the iris and the crystalline lens). The invention also relates to a device and an ultrasound probe which allow this investigation and this display to be achieved in 2D or 3D.

In ultrasound imaging and more particularly in medical echography, the choice of frequency is dictated by the compromise between resolution and penetration depth. Specifically, because of the increase in attenuation of ultrasound waves with frequency, the penetration depth of ultrasound increases with decreasing frequency. However, the image resolution decreases with decreasing frequency.

Processes are known, in particular through patent FR 2,620,327, for the investigation of ocular structures, by echography, using probes operating at low frequencies of the order of 10 MHz, and focused to a depth roughly equal to the size of an ocular globe (about 23 to 25 mm). These processes mean, on one hand, that images in section of the posterior segment of the eye can be achieved with spatial resolutions of the order of a millimetre and, on the other hand, that a very rough examination of the entire anterior segment of the eye can be carried out.

The major drawback of low-frequency echography is mainly the low resolution (600 to 700 μm) provided by these low frequencies, which do not allow detailed

analysis of the retina and the other layers of the posterior wall of the eye (choroid and sclera) and more particularly in the macular region.

In order to increase both the lateral and axial resolution, investigation and display processes using ultrasound probes at high frequency, of the order of 50 to 100 MHz (cf. US 5,551,432 and C.J. PAVLIN, M.D. SHERAR, F.S. FOSTER: "Subsurface ultrasound microscopic imaging of the intact eye", Ophthalmology 97: 244, 1990), with a short focal length (of about 4 to 8 mm), have enabled the use, with a resolution of 50 μm, of structures of the anterior segment of the eye, to depths of the order of 5 mm, or of structures of the peripheral retina which are very close to the anterior segment.

In conclusion, it is therefore accepted that the use of high frequencies seems to be limited to investigation of the anterior segment and the peripheral retina, whereas investigation of the deep structures (posterior segment) requires the use of much lower frequencies, while only providing very low spatial resolutions, of a few hundred microns.

The present invention aims to alleviate the drawbacks of the known processes of the prior art, by proposing an investigation and display process using a high-frequency ultrasound probe which combines both very high spatial resolution and a field of investigation covering the anterior and posterior segments of the ocular globe.

To this end, the process for the investigation and display of tissues of human or animal origin is characterized in that:

- an ultrasound probe is positioned, said probe being carried by a head steered by means of a three-dimensional positioning system, in particular a system controlled by a computer at right angles to said tissue structure,

- the probe is controlled such that it generates beams of convergent high-frequency ultrasound

waves, these waves being focused on a given area of tissue structure,

- the tissue structure is scanned by the positioning system steered by the computer, while said computer carries out, in parallel, the acquisition of the signals reflected by the tissue structure,

- various signal processing operations are carried out on the data coming from the scanning, to improve the reproduction of the information and to facilitate the interpretation thereof by the practitioner.

According to another advantageous characteristic of the invention, the probe is excited such that it generates wave beams whose nominal frequency is included within the range from 30 to 100 MHz with a broad bandwidth, adapted to the frequencies reflected by the structure investigated.

According to yet another advantageous characteristic of the invention, the wave beams are focused over a vertical penetration distance of between 20 and 30 mm.

Other characteristics and advantages of the present invention will emerge from the description given hereinbelow, with reference to the appended drawings which illustrate an entirely non-limiting embodiment of the invention. In the figures:

- Figure 1 is a synoptic view of a device enabling the process forming the subject of the invention to be implemented;

- Figure 2 is a view illustrating a use of the process forming the subject of the invention for the investigation of the posterior segment of an ocular globe;

- Figure 3 is a view illustrating a use of the process forming the subject of the invention for the investigation of the anterior segment of an ocular globe;

- Figures 4a and 4b illustrate, on one hand, a front view of one embodiment of the ultrasound probe

consisting of an annular array whose focus point can be modified electronically and, on the other hand, a side view of this same probe into which a phase difference has been introduced at transmission or at reception between the various rings making up the array;

- Figure 5 is a view illustrating a use of the process forming the subject of the invention for the investigation of the anterior segment of an ocular globe, using a dynamic focusing probe;

- Figure 6 is a view illustrating a use of the process forming the subject of the invention for the investigation of the posterior segment of an ocular globe, using a dynamic focusing probe;

- Figure 7 shows a comparison between a macular section of a human globe *in vitro*, obtained by macroscopic histological imaging (right side) and an image arising from the process forming the subject of the invention (left side) where P represents the retinal folds, R the retina, S the sclera and V the vitreous humour;

- Figure 8 is the image obtained from an anterior segment of a rabbit's eye, by the process forming the subject of the invention, where C represents the cornea, I the iris, S the sclera and Cr the anterior surface of the lens.

According to a preferred embodiment of the process forming the subject of the invention, of which one system enabling its implementation is shown schematically in Figure 1, the process consists in positioning an ultrasound probe 1 mounted within a head articulated in three dimensions X, Y, Z, at least one direction of which can be fixed, this head being steered by a servo-controlled positioning system 2, controlled by a computer 3, in particular in a direction perpendicular to the medium to be investigated.

This ultrasound probe 1 consists mainly of a transducer, in particular one made of PVDF (polyvinylidene difluoride), controlled by a

transmitter/receiver 4, in order to generate beams of convergent, broadband, ultrasonic waves, these waves being able to adopt a spherical or linear profile.

Next, Figure 2 shows an investigation of the posterior segment of an ocular globe 5, previously inserted into a coupling medium 6 which does not impair the propagation of the waves, especially in the retina region. A probe 1 positioned on the pars plana 7 is used to avoid absorption of the ultrasound beam by the lens 8 (this lens also marking the boundary between the posterior segment 9 and the anterior segment 10 of an ocular globe 5). This probe 1 transmits beams of ultrasound waves set within a nominal broadband frequency range varying from 30 to 100 MHz, involving wavelengths going from 50 to 15 μm, focused at a focal length of between 20 and 30 mm and preferably 25 mm, corresponding in fact to a focus at an average depth of an ocular globe.

For example, for a probe with a nominal frequency of 50 MHz, lateral and axial resolutions of 220 and 70 μm respectively are obtained at the focal length.

The receiving system will have a bandwidth adapted to the frequencies reflected by the structure, these frequencies being lower than the transmitted frequencies because of the attenuation by the medium which is crossed.

In order to investigate the anterior segment (cf. Figure 3), this same probe 1 is used under the same control conditions as previously, in a position offset on the vertical axis (Z axis) at a distance corresponding in fact to the previous focal length.

According to another embodiment, the focal length, especially on the vertical penetration axis, is not modified by a mechanical servocontrol 2 in the position, but by an electronic or digital device steering the probe and able to modify, by careful command, the focusing area of the probe, in order thus to obtain simultaneously a high resolution image of the

anterior segment and of the posterior segment of the eye. This probe, with dynamic focusing carried out by an electronic or digital control process, consists of a multi-element probe, with circular symmetry, made up of several concentric annular transducers evenly spaced over a plane surface or with spherical concavity (refer to Figure 4a). These transducers are independent of each other and are controlled individually in transmission and in reception by pulses which are offset in time (refer to Figure 4b which shows dynamic focusing obtained by introducing a phase difference - time delay - into the transmission between the various rings).

In transmission, the generated wavefront is convergent and its curvature is modified according to the distance between the structure investigated and the probe. The peripheral rings transmit first and the excitation of the central ring is the most retarded. Thus the focal length along the axis of the probe can be varied and is therefore determined by the phase difference or the time delay introduced between the various transducers. The same principle of dynamic focusing is used in reception: the electronic delay is adjusted to the depth of the echoes which arrive at that moment at the probe. In this way the depth of field is increased without in any way degrading the lateral resolution.

A measurement system, of which each of the components (digitizer 11, computer 3, control electronics 2, transmitter/receiver 4, etc.) forming it has a bandwidth compatible with the processing and analysis of the signals originating from the anterior segment and/or of the signals coming from the posterior segment of the eye, enables processing of the signals backscattered by the structure investigated. Thus, the backscattered ultrasound signal is amplified then digitized using the digitizer 11, at a given sampling frequency (in particular of the order of 400 MHz over 8 bits).

This same computer controls the stepper on DC motors in order to move the probe and scan the ultrasound beams over the sample in a defined step along X and along Y in order to allow another measurement point or in an R,Ω step using a probe support head which allows an arciform scan.

For *in vivo* measurements and investigations, it is necessary, in order to get round the problem of parasitic movements of the eye in its orbit, to process the signal in real time and to have available an extremely fast and accurate probe movement system.

According to another characteristic, the computer is fitted with a module for processing the image and the radiofrequency signal. This module has programmed software which enables the two quantitative approaches, of 2D and/or 3D biometry and of tissue characterization, to be carried out.

The echographic signal can be shown in real time in the form of a A-scan line or in the form of a 2D image of the B-scan type. The B-scan images can display sections in the various planes parallel to the direction of propagation of the ultrasound (cf. Figures 7 and 8). A 2D image of the C-scan type can also be calculated in order to display sections in the plane perpendicular to the direction of propagation of the ultrasound. The C-scan is able to show sections located at different depths of the whole ocular globe.

The calculation and the reconstruction of the 3D image can be carried out using programmed mathematical functions specific to the ultrasound data to be processed.

Thus, provided the propagation speed of the ultrasound in the structures investigated is known, it is possible to determine morphological characteristics of these structures, especially their thickness and/or their volume.

The processing software of the radiofrequency signal enables a frequency analysis of the digitized and recorded backscattered signals to be made in order

to calculate quantitative ultrasound parameters for the purpose of tissue characterization. These parameters are in particular the attenuation coefficient in dB/cm.MHz (decibels/cm.megahertz), the overall attenuation coefficient in dB/cm, the backscatter coefficient in dB/cm.MHz and the overall backscatter coefficient in dB/cm.

These parameters can be estimated locally and their values can be shown in the form of images (parametric images).

It is of course possible to add other algorithms for processing the radiofrequency signal and the image, algorithms which could produce quantitative morphological and/or tissue information capable of characterizing the structures of the eye.

The images obtained by this investigation process, both for an ocular globe and the region of the anterior segment and the posterior segment, have a resolution which is improved by a factor of at least two to three compared with that obtained with conventional echographs and are not limited by the transparency of the media investigated as in particular with conventional optical investigation means (biomicroscopy, angiography) whose quality can be affected by the presence of cataracts and haemorrhages.

By way of example, Figure 7 illustrates the similarities between a histological image and an echographic image of the macula of a human eye (*in vitro*), and Figure 8 illustrates an image of an anterior segment of a rabbit's eye.

The process and the device which enables its implementation, such as those described previously, are not limited to applications in ophthalmology, but they can also find applications in gynaecology and obstetrics, in gastro-enterology and in the field of cardio-vascular examinations and examinations by coelioscopy, or in dermatology and more generally in any medium which reflects a usable signal.

In particular, in the field of dermatology, it is possible, using the investigation and display process forming the subject of the invention, to investigate the various thicknesses of tissue forming the skin. Thus, it is possible for example, by processing the signal, to assess the degree of skin hydration, to evaluate healing of a tissue, to localize and investigate a tumour, and finally, more generally, to to open the way to examining a large number of pathologies currently encountered in dermatology.

The focus point or focusing area of the wave beam will be adjusted within a range going from a few tenths of a millimetre to several millimetres and the waveband used will be between 30 and 100 MHz.

It is of course understood that the present invention is not limited to the embodiments described and shown hereinbefore, but that it encompasses all the variants thereof.

CLAIMS

1. Process for the investigation and display of tissues of human or animal origin, characterized in that:

- an ultrasound probe is positioned, said probe being carried by a head steered by means of a three-dimensional positioning system, in particular a system controlled by a computer at right angles to said tissue structure,

- the probe is controlled such that it generates beams of convergent high-frequency ultrasound waves, these waves being focused on a given area of tissue structure,

- the tissue structure is scanned by the positioning system steered by the computer, while said computer carries out, in parallel, the acquisition of the signals reflected by the tissue structure,

- various signal processing operations are carried out on the data coming from the scanning, to improve the reproduction of the information and to facilitate the interpretation thereof by the practitioner.

2. Process according to Claim 1, characterized in that the probe is excited such that it generates wave beams whose nominal frequency is included within the range from 30 to 100 MHz with a broad bandwidth, adapted to the frequencies reflected by the structure investigated.

3. Process according to Claim 1 or 2, characterized in that the wave beams are focused over a vertical penetration distance of between 20 and 30 mm.

4. Process according to any one of the preceding claims, characterized in that it is applicable to the investigation of a posterior segment of an ocular globe.

5. Process according to any one of the preceding claims, characterized in that it is applicable to the

investigation of an anterior segment of an ocular globe.

6. Process according to any one of the preceding claims, characterized in that it is applicable to the investigation of a human ocular globe.

7. Process according to any one of the preceding claims, characterized in that it is applicable in gynaecology and obstetrics, in gastro-enterology and in the field of cardio-vascular examinations and examinations by coelioscopy, or in dermatology and more generally in any medium which reflects a usable signal.

8. System for the implementation of the process according to any one of the preceding claims, characterized in that it comprises an ultrasound probe (1) mounted within a head articulated in three dimensions, possibly controlled by a computer (3), in a direction in particular perpendicular to the medium to be investigated, this probe (1) consisting of a transducer, controlled by a transmitter/receiver (4), in order on the one hand to generate and focus the beams of convergent, broadband, ultrasonic waves onto the tissue structure to be scanned and investigated, by means of a coupling medium (6), and on the other hand to collect the signals reflected by said structure for the purpose of processing them, in particular by the computer (3), with a view to subsequent interpretation.

9. System according to Claim 8, characterized in that the focal length of the ultrasound probe (1) is modified by an electronic or digital device which controls said probe carefully, in order to adjust the focus point of said probe.

10. System according to Claim 8, characterized in that the focal length of the ultrasound probe (1) is modified mechanically by the servocontrolled positioning system (2).

11. System according to Claim 8, characterized in that the computer (3) controls stepper motors in order to move the probe (1) and scan the ultrasound beams

over the tissue structure in an R,Ω step, using a probe support head which allows an arciform scan.

12. System according to Claim 8, characterized in that the computer (3) controls stepper motors in order to move the probe (1) and scan the ultrasound beams over the tissue structure in an X,Y,Z step, using a probe support head which allows a cartesian scan.

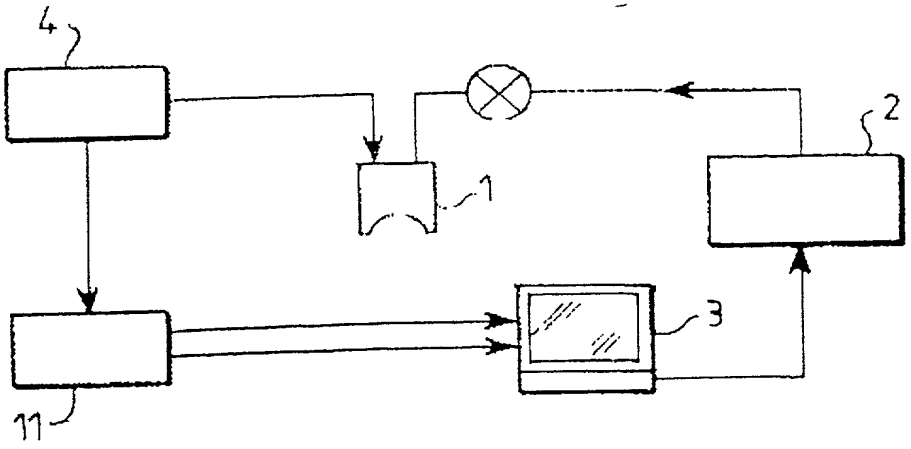


FIG.1

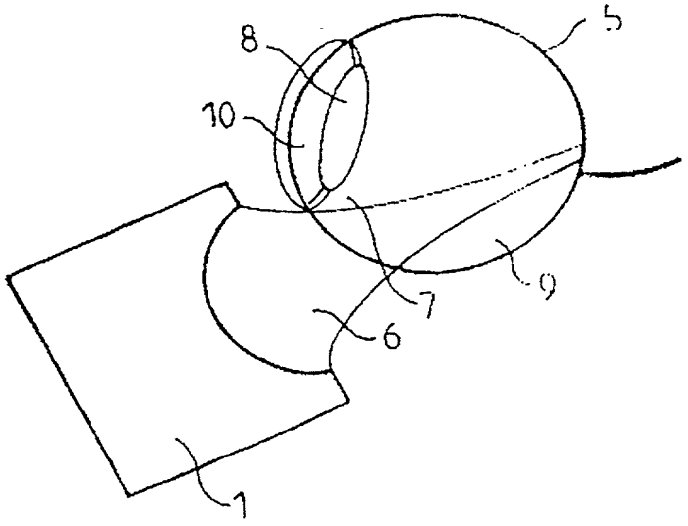


FIG.2

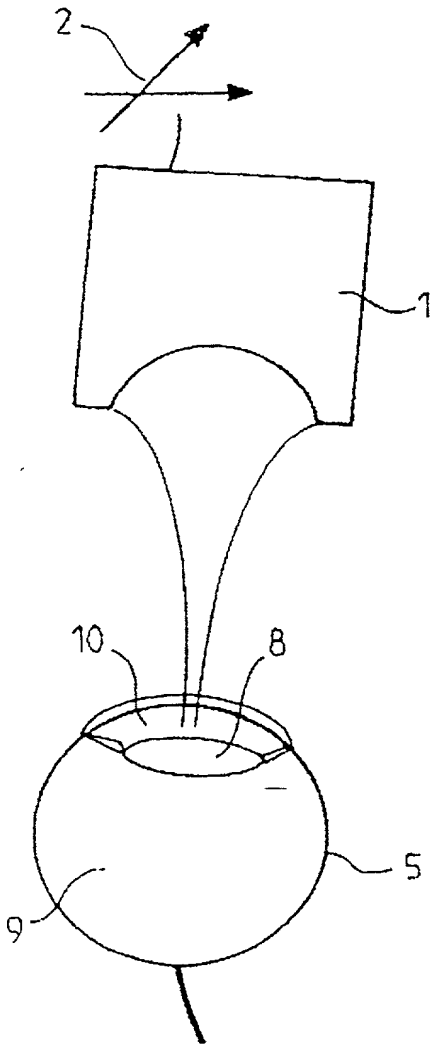


FIG.3

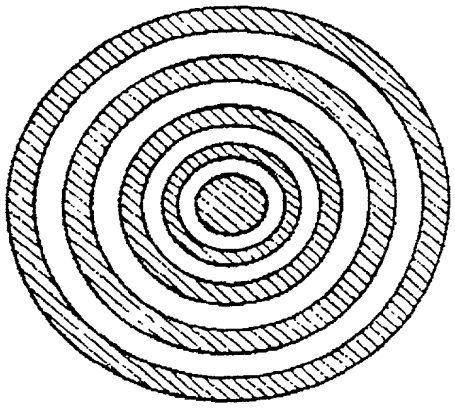


FIG.4a

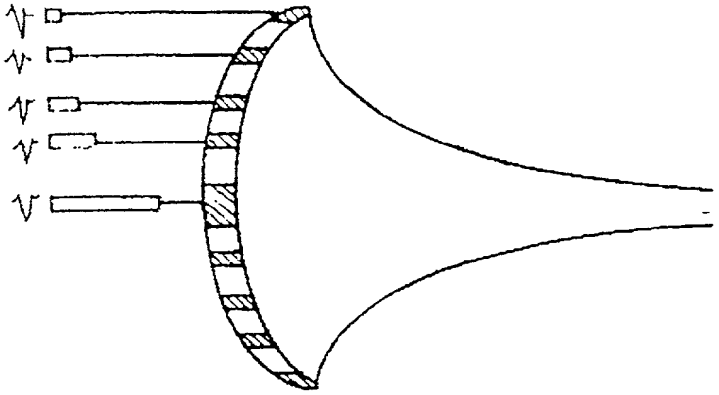


FIG.4b

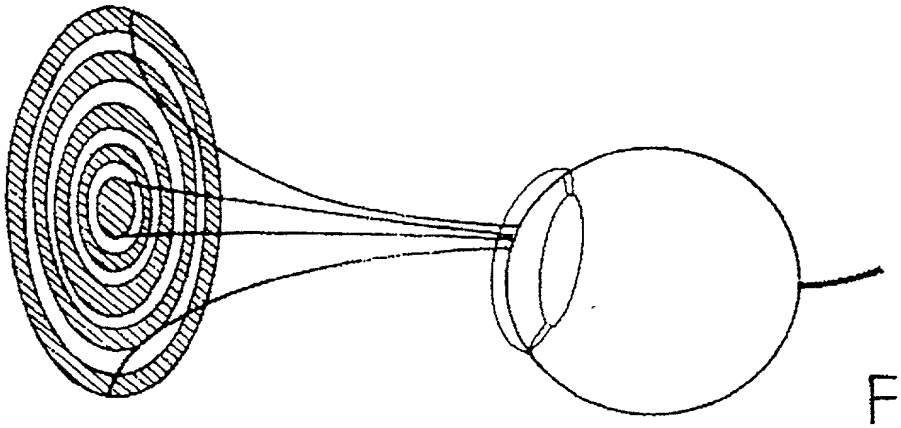


FIG.5

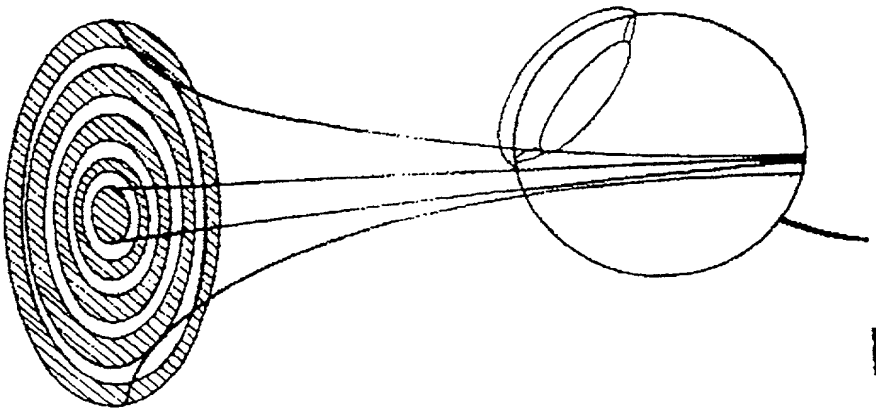
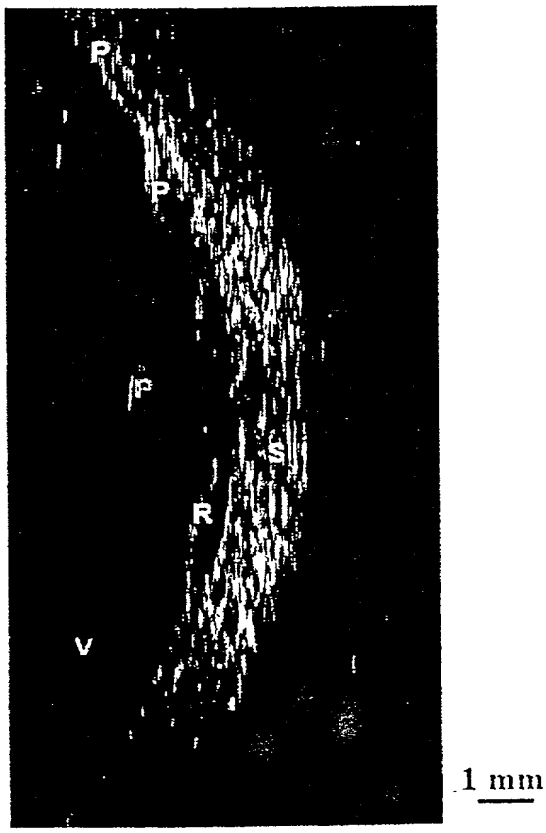


FIG.6



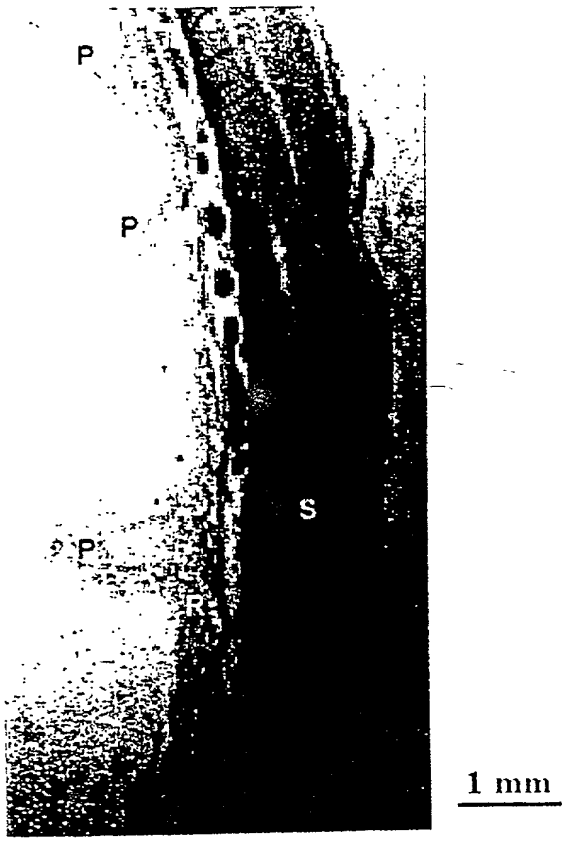


Figure 7

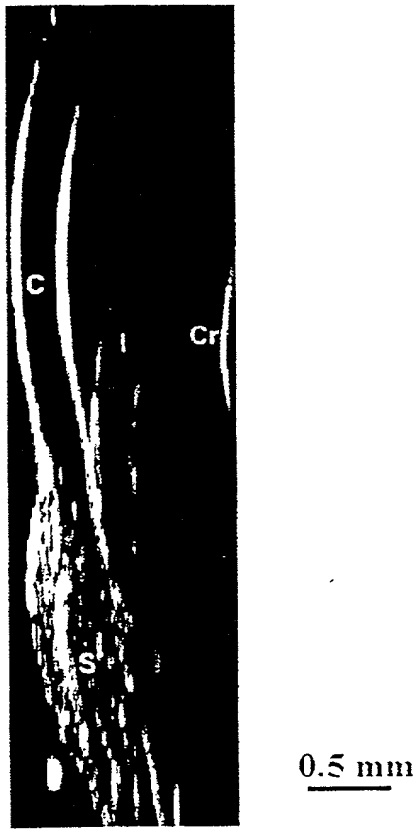


Figure 8

DECLARATION FOR PATENT APPLICATION

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: Method for exploring and displaying tissues of human or animal origin from a high frequency ultrasound probe.

the specification of which: (check one)

[ ] is attached hereto. [X] was filed on January 12, 1999 as ~~United States Patent Application Serial No.~~ or PCT International Application Number PCT/FR99/00040, and was amended on March 20, 2000 (if applicable). and on May 29, 2000

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 CFR § 1.56(a).

Prior Foreign Application(s): I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

			Priority Claimed
98 00209 (Application No.)	FRANCE (Country)	12 January 1998 (Day/Month/Year Filed)	[X] Yes [ ] No
(Application No.)	(Country)	(Day/Month/Year Filed)	[ ] Yes [ ] No
(Application No.)	(Country)	(Day/Month/Year Filed)	[ ] Yes [ ] No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by 35 U.S.C. § 112, first paragraph, I acknowledge the duty to disclose material information as defined in 37 CFR § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(U.S. Application Serial No.)	(U.S. Filing Date)	(Status--patented, pending, abandoned)
(U.S. Application Serial No.)	(U.S. Filing Date)	(Status--patented, pending, abandoned)

I hereby appoint Elliott I. Pollock, Registration No. 16,906; George Vande Sande, Registration No. 17,276; Robert R. Priddy, Registration No. 20,169; Burton A. Amernick, Registration No. 24,852; Stanley B. Green, Registration No. 24,351; Richard Wiener, Registration No. 18,741; Townsend M. Belser, Jr., Registration No. 22,956; Morris Liss, Registration No. 24,510; Martin Abramson, Registration No. 25,787; George R. Pettit, Registration No. 27,369; Louis Woo, Registration No. 31,730; Elzbieta Chlopecka, Registration No. 32,767; Eric J. Franklin, Registration No. 37,134; and Robert Scott Wales, Registration No. 39,413, my attorneys with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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over

DECLARATION FOR PATENT APPLICATION

Page Two

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Citizenship _____

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Full name of sixth joint inventor (if any): _____

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Full name of seventh joint inventor (if any): _____

Inventor's Signature _____ Date _____

Residence Address _____

Citizenship _____

Post Office Address _____

Full name of eighth joint inventor (if any): _____

Inventor's Signature _____ Date _____

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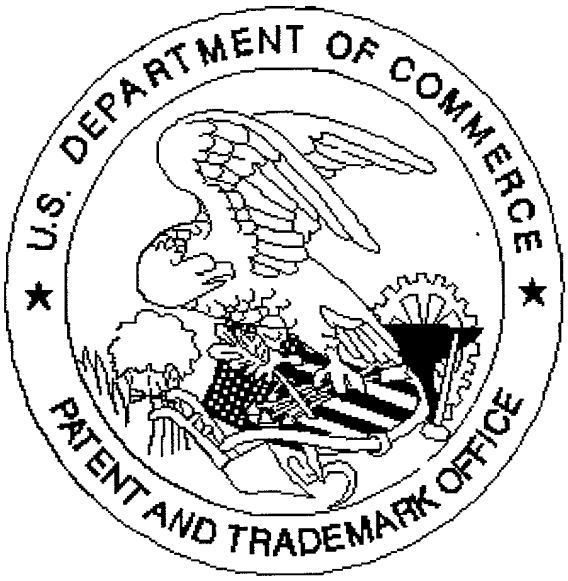

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